ehp Environmental Health PERSPECTIVES
ehponline.org
Published by the National Institute of Environmental Health Sciences

Assessing Susceptibility from Early-Life Exposure to Carcinogens

Hugh A. Barton, V. James Cogliano, Lynn Flowers, Larry Valcovic, R. Woodrow Setzer, Tracey J. Woodruff

doi:10.1289/ehp.7667 (available at http://dx.doi.org/)
Online 7 April 2005

The National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services

Assessing Susceptibility from Early-Life Exposure to Carcinogens

Authors:

Hugh A. Barton[1]
V. James Cogliano[2]
Lynn Flowers[3]
Larry Valcovic[3]
R. Woodrow Setzer[1]
Tracey J. Woodruff[4]

[1]Office of Research and Development, National Center for Computational Toxicology, U.S. Environmental Protection Agency, Research Triangle Park, NC
[2] Office of Research and Development, U.S. Environmental Protection Agency, present address: International Agency for Research on Cancer, Lyon, France
[3] Office of Research and Development, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Washington, DC
[4]Office of Policy, Economics, and Innovation, U.S. Environmental Protection Agency, San Francisco, CA

Corresponding author and to whom page proofs should be sent:

Tracey J. Woodruff
US EPA
75 Hawthorne St, SPE-1
San Francisco, CA 94105
Phone: 415.947.4277
Fax: 415.947.3519
woodruff.tracey@epa.gov

Keywords: cancer, children, mode of action, risk assessment, susceptible populations, early-life exposure, exposure

Acknowledgments

We would like to thank David Bennett for his work in leading the initial efforts for this work, Bill Wood for his support, and Julian Preston and Suzanne Fenton for their helpful reviews of the document. Special thanks to Rosemary Castorina, Neepa Choksi, Rebecca Brown, Ellen Phelps Donovan, Nyree Bekarian, and Brad Hurley for their efforts in compiling the underlying information. The authors declare they have no competing financial interests.

Disclaimer

This document does not constitute U.S. Environmental Protection Agency policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

Definitions

Perinatal is defined as the time around birth and may include both prenatal (prior to birth) and early postnatal (after birth) effects.

Susceptibility is defined here as an increased likelihood of an adverse effect, often discussed in terms of a factor that can be used to describe a human subpopulation (e.g., lifestage, demographic feature, or genetic characteristic). The terms "susceptibility" and "sensitivity" are used with a variety of definitions in published literature making it essential that readers are aware of these differences in terminology across documents.

List of Abbreviations

3-MC	3- methylcholanthrene
3'ME-DAB	3-Methyl-4-dimethylaminoabenzene
AAB	4-Acetylaminobiphenyl
AB	4-Aminoazobenzene
ABSS	Atomic Bomb Survivor Study
Ah	Aryl hydrocarbon
AZT	3'-Azido-3'-deoxythymidine
B[a]P	Benzo(a)pyrene
BBN	N-Butyl-N-(3 hydroxbutyl)nitrosamine
BCPN	N-Butyl-N-(3-carboxypropyl)nitrosamine
BPH	1-(4'Bromophenylazo)-1-phenyl-1-hydroperoxymethane
BNU	Butylnitrosourea
DBA	Dibenzanthracene
DBN	Dibutylnitrosamine
DDT	Dichlorodiphenyltrichloroethane
DEN	Diethylnitrosamine
DES	Diethylstilbesterol
DMBA	Dimethylbenz(a)anthracene
DMH	1,2-Dimethylhydrazine
DMN	Dimethylnitrosamine
DNA	Deoxyribonucleic acid

DPH	Diphenylhydantoin
EHP	Environmental Health Perspectives
ENU	Ethylnitrosourea
ERR	Excess relative risk
ETU	Ethylene thiourea
FAA	N-2-Fluorenylacetamide
Glu-P-1	2-Amino-6-methyldipyridol[1,2-a:3',2'-d]imidazole
Glu-P-2	2-Aminodipyridol[1,2-a:3',2'-d]imidazole
IP	Intraperitoneal
LET	Linear energy transfer
MNNG	1-Methyl-3-nitro-1-nitrosoguanidine
MNU	Methylnitrosourea
NNK	4-(Methylnitrosoamino)-1-(3-pyridyl)-1-butanone
N-OH-AAB	3-Hydroxyl-4-acetylaminobiphenyl
N-OH-FAA	N-2-hydroxy-N-2-fluorenylacetamide
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
PBB	Polybrominated biphenyl
SAR	Structure-activity relationship
SD	Standard deviation
SKF 525A	2-diethylaminoethyl-2,2-dephenylvalerate hydrochloride

Outline

Abstract

Cancer risk assessment methods currently assume children and adults are equally susceptible from exposure to chemicals. We reviewed available scientific literature to determine whether this was scientifically supported. We identified over 50 chemicals causing cancer following perinatal exposure. Human data are extremely limited, with radiation exposures showing increased early susceptibility at some tumor sites. Twenty-seven rodent studies for 18 chemicals had sufficient data following postnatal and adult exposures to quantitatively estimate potential increased susceptibility from early-life exposure, calculated as the ratio of juvenile to adult cancer potencies for three study types: acute dosing; repeated dosing; and lifetime dosing. Twelve of the chemicals act through a mutagenic mode of action. For these, the geometric mean ratio was 11 for lifetime exposures and 8.7 for repeat exposures, with a ratio of 10 for these studies combined. The geometric mean ratio for acute studies is 1.5, which was influenced by tissue specific results [geometric mean ratios for kidney, leukemia, liver, lymph, mammary, nerve, reticular tissue, thymic lymphoma, and uterus/vagina were greater than one (range 1.6 – 8.1); and forestomach, harderian gland, ovaries, and thyroid were less than one (0.033 – 0.45)). Chemicals causing cancer through other modes of action indicate some increased susceptibility from postnatal exposure (geometric mean ratio 3.4 for lifetime exposure and 2.2 for repeat exposure). Early exposures to compounds with endocrine activity sometimes produce different tumors following exposures at different ages. These analyses suggest increased susceptibility to cancer from early-life exposure, particularly for chemicals acting through a mutagenic mode of

action.